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An observational, prospective, two-cohort comparison of a fixed versus variable dosing strategy of prothrombin complex concentrate to counteract vitamin K antagonists in 240 bleeding emergencies

Nakisa Khorsand,¹ Nic J.G.M. Veeger,² Reinier M. van Hest,^{1,3} Paula F. Ypma,⁴ Jeroen Heidt,⁵ and Karina Meijer⁶

¹Department of Hospital Pharmacy, Haga Teaching Hospital, The Hague; ²Department of Epidemiology, University Medical Centre, Groningen; ³Department of Clinical Pharmacy, Academic Medical Center, Amsterdam; ⁴Department of Haematology, Haga Teaching Hospital, The Hague; ⁵Department of Internal Medicine, Medical Centre Haaglanden, The Hague; and ⁶Division of Haemostasis and Thrombosis, Department of Haematology, University Medical Centre Groningen, The Netherlands

ABSTRACT

Background

Despite years of experience with vitamin K antagonist-associated bleeding events, there is still no evidence to help identify the optimal treatment with prothrombin complex concentrates. Variable dosing and fixed dose strategies are being used. In this observational prospective two-cohort study, we aimed to assess the non-inferiority of a low fixed PCC dose (1,040 IU Factor IX) compared to the registered variable dosing regimen based on baseline International Normalized Ratio, bodyweight, and target International Normalized Ratio, to counteract vitamin K antagonists in a bleeding emergency in a daily clinical practice setting.

Design and Methods

Non-inferiority of the fixed prothrombin complex concentrate dose was hypothesized with a margin of 4%. Main end points were proportion of patients reaching the target International Normalized Ratio (< 2.0) after prothrombin complex concentrate treatment, and successful clinical outcome.

Results

Target International Normalized Ratio was reached in 92% of the fixed dose patients (n=101) versus 95% of variable dose patients (n=139) resulting in a risk difference of -2.99% (90% CI: -8.6 to 2.7) (non-inferiority not confirmed). Clinical outcome was successful in 96% and 88% of fixed versus variable dose, respectively, with a risk difference of 8.3% (90% CI: 2.7-13.9; non-inferiority confirmed).

Conclusions

Although a lower fixed prothrombin complex concentrate dose was associated with successful clinical outcome, fewer patients reached the target International Normalized Ratio.

Key words: anticoagulation, hemorrhage, prothrombin complex concentrate, reversal, vitamin K antagonist reversal.

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Correspondence: Nakisa Khorsand, Haga Teaching Hospital, Leyweg 275, 2545 CH, The Hague, The Netherlands. Phone: international +31.70.3217268. Fax: international +31.70.3217156. E-mail: n.khorsand@hagaziekenhuis.nl

The online version of this article has a Supplementary Appendix.

Introduction

Millions of patients receive vitamin K antagonist (VKA) therapy worldwide. Although highly effective, risk of bleeding is an important limitation. When a major bleed occurs, rapid reversal of VKA is required. Despite 60 years of experience with VKA and VKA-associated bleeding events, their treatment is still a subject of debate. Either fresh frozen plasma (FFP) or prothrombin complex concentrate (PCC) are infused to administer the depleted coagulation factors.

Based on studies showing that PCC reverses VKA therapy more rapidly and more completely than a standard dose of FFP,¹ several expert consensus panels have recommended the use of PCC.²⁻⁴ Unfortunately, an optimal dosing strategy for PCC has not been established, and whether or not a low fixed dose can be applied is still under discussion.⁵⁻⁷

Furthermore, lingering perceptions regarding the thrombotic risk associated with PCC products in hemophiliacs, in addition to limited licensing of PCC products for VKA reversal, have stopped clinicians in many countries from using PCC for this purpose.⁸⁻¹⁰

Although PCC treatment for VKA reversal in bleeding patients is different from PCC treatment in hemophiliacs with respect to dosing frequency, the lowest possible dose should still be considered.

In a pilot setting, we showed a promising effect of a low fixed dose of 1,040 IU F IX to rapidly counteract VKA therapy.¹¹ In this study, a trend was observed towards a marginally lower proportion of patients who reached the target International Normalized Rate (INR) after treatment with the fixed dose regimen compared to variable doses. Variable dosing is recommended by the manufacturer and is based on patient weight, baseline INR, and target INR. In the pilot study, results on clinical outcome were comparable. The present prospective study was, therefore, carried out to formally assess the non-inferiority of the low fixed dose regimen of 1,040 IU FIX *versus* the variable dose regimen of PCC for VKA reversal in bleeding patients.

Design and Methods

Study design

This prospective, observational two-cohort study compares the outcome of treatment with PCC for VKA reversal according to two different dosing strategies in two Dutch teaching hospitals. Both hospitals are located close to each other in one Dutch city. These hospitals are comparable regarding total number of beds, the size of the Emergency Department, Intensive Care Unit (ICU), and Traumatology, Surgery, and Internal Medicine Departments.

Patients

Patients were eligible for inclusion if reversal of VKA treatment with PCC was indicated for major or clinically relevant, non-intracranial bleeding. Patients with an indication for PCC because of an intracranial bleeding event, an urgent invasive procedure, and patients not using VKA treated with PCC were excluded.

Prothrombin complex concentrate regimen

Both participating hospitals used Cofact® (Sanquin BV, Amsterdam, The Netherlands) as PCC. This product contains factors II, VII, IX and X. Cofact does not contain either activated fac-

tors or heparin. Stocks of this product were adequate and promptly available in both hospitals.

The participating hospitals applied different PCC dosing strategies in routine clinical practice. Patients entering one hospital were treated with a low fixed dose of 1,040 IU F IX. The other hospital applied a variable dose regimen (*Online Supplementary Table S1*) based on patient body weight, the baseline INR, and target INR. After the initial dose infusion, the attending physician evaluated VKA reversal. It was at the discretion of the physician whether to administer additional PCC at any moment, e.g. in case of a high INR after treatment, deterioration in patient condition, or an ongoing active bleeding event. In both cohorts, all patients received 10 mg vitamin K intravenously along with the PCC infusion.

Because both dosing strategies were part of the protocol of the local hospital, the institutional ethics committee waived the need for informed consent.

Study end points

The primary end point was the proportion of patients who achieved the target INR at 15 min after PCC infusion. Target INR was below 2.0, which is accordance with Dutch routine practice for rapid correction of INR in non-cranial bleeding emergencies.

The secondary end point was the proportion of patients with successful clinical outcome as judged by the attending physician. Successful clinical outcome was confirmed when visual bleeding had stopped, no further decrease in hemoglobin was observed, blood pressure was normalized, and no further PCC or blood transfusion was given. This definition is in line with that proposed by the International Society of Thrombosis and Haemostasis.¹²

Time between entry into the emergency department and start of the PCC infusion, the reached INR after PCC infusion, and the administered PCC dose were also analyzed.

Finally, information regarding complications during hospitalization was recorded. This included mortality, bleeding complications, deep vein thrombosis (DVT), pulmonary embolism (PE), myocardial infarction (MI), and ischemic cerebrovascular events.

Data collection

In both hospitals, PCC was distributed and registered by the hospital's blood bank when ordered for an individual patient. After registration, the study coordinator was immediately notified by an automatic signal, and was able to prospectively follow the patient from that moment on.

For the included patients, level of anticoagulation was measured prior to and 15 min after PCC treatment. Clinical outcome was assessed by the attending physician.

Baseline status and patients' characteristics were evaluated using medical chart data at admission. These included age, gender, concomitant drug use, indication for VKA and duration of VKA therapy, baseline INR, the site of bleeding, administration of vitamin K, and admission to the ICU. We also evaluated patient health status and the existence of co-morbidities based on the Charlson Comorbidity Index^{13,14} and the patient's history of bleeding complications.

In both hospitals, level of anticoagulation was assessed by INR measurement using Stacompact® (Roche diagnostics) and Hepatoquick® reagents (Stago) with an instrument specific ISI value of 0.92. The INR is expressed in a number up to a value of 7.6. All INR values above 7.6 were reported as "above 7.6" in accordance with hospital protocol.

Information regarding invasive and non-invasive treatment of the bleeding other than PCC administration, time between entry into the emergency department and PCC infusion, and complications during hospitalization was collected prospectively by daily follow up until discharge or death.

Statistical analysis

We hypothesized that a fixed dose regimen was non-inferior to a variable dose regimen within a margin of 4% difference in proportion to the patients reaching the target INR, presuming target INR is achieved in 99% of the patients treated with the variable dosing regimen.

Based on the above hypothesis, it was calculated that two equal cohorts of 106 patients were required to achieve a power of 90% with an alpha of 5% (one-sided).

Non-inferiority analysis for the proportion (risk) difference was performed using an asymptotic Wald test for non-inferiority with the non-inferiority limit set to 4%. In this, also asymptotic Wald confidence limits were calculated. In addition, differences between cohorts were evaluated using Student's t-test or Mann-Whitney test for continuous data, depending on normality of data, and the Fisher's exact test for categorical data.

Subgroup analysis was planned for patients with a baseline INR above and below 5.

$P < 0.05$ (two-sided) was considered statistically significant. Commercially available computer software (IBM® SPSS® Statistics version 19 and Statistical Analysis System 9.2; SAS Institute, Cary, NC, USA) was used for all analyses.

Results

Patients' characteristics

Consecutive patients were enrolled in both cohorts from November 2007 to July 2010.

During this period, 101 patients were included in the fixed dose cohort and 139 patients in the variable dose cohort. Ten patients presented with a second bleed during the study period and were not re-enrolled.

Both cohorts were comparable with regard to age, gender, weight, relevant co-medication, Charlson Comorbidity Index, and the indication for VKA treatment. In both cohorts, the VKA phenprocoumon was the most commonly used (88% vs. 84% of patients in the fixed dose and the variable dose cohort, respectively). The mean duration of hospitalization, during which patients were followed up, was six days. Main patients' characteristics are shown in Table 1.

Prothrombin complex concentrate treatment

The range of concentration of the vitamin K dependent factors in PCC batches used during the period of evaluation was 23-26 IU F IX, 10-14 IU F VII, 19-24 IU F II, and 18-23 IU F X mL⁻¹; 26 IU FIX per mL was used for dose calculation.

The most frequent indication for PCC treatment was gastrointestinal bleeding (57% in each cohort; $P = 0.73$) (Table 2). In both cohorts, the severity of bleeding complications and the additional treatment besides PCC were highly comparable whereas no differences were observed in transfusion of red blood cells and FFP, endoscopic treatment of the gastrointestinal bleeding, performance of any other surgery to stop non-gastrointestinal bleedings, and ICU admissions (Table 2).

Dosage used in the fixed dose cohort was 1,040 IU F IX and non-adherence to this dosage occurred in 32 (32%) patients. Of these, 29 patients had a lower dose than the fixed dose, with a median of 520 IE, and 3 patients received a higher dose ($n = 1$, 1,300 IE; $n = 2$, 1,560 IE).

In the variable dosing regimen, the median PCC dosage per patient was 1,560 IU F IX (range 520-523,120 IU F IX;

$P < 0.001$) (Figure 1). In the fixed dose cohort, a second PCC infusion was required in 3 (3.0%) patients versus 4 (2.9%) patients in the variable dose regimen cohort ($P = 1.00$).

International Normalized Ratio

Target INR was achieved in 91.7% versus 94.7% of

Table 1. Patients' characteristic.

	Fixed dose (n=101)	Variable dose (n=139)	P value
Male, N (%)	50 (50%)	71 (51%)	0.90
Age in years, median (range)	77 [37-95]	79 [23-98]	0.18
Weight in kg, median (range)	72 [36-136]	75 [43-154]	0.80
VKA is phenprocoumon, N (%)	89 (88%)	117 (84%)	0.46
Malignancy, N (%)	31 (31%)	37 (27%)	0.56
Concomitant other antithrombotic agents, N (%)	22 (22%)	34 (24%)	0.65
Charlson Comorbidity Index (SD)	2.93 (2.1)	2.71 (1.7)	0.49
Indication for VKA therapy, N (%)			0.71
- Atrial fibrillation	57 (56%)	84 (60%)	
- Venous thromboembolism	20 (20%)	19 (14%)	
- Heart valve replacement	9 (9%)	17 (12%)	
- Myocardial infarction	7 (7%)	9 (6%)	
- Other	8 (8%)	10 (7%)	
Time since start VKA < 3 months, N (%)	12 (12%)	24 (17%)	0.28
History of bleeding, N (%)	26 (26%)	46 (33%)	0.25
Baseline INR, median (range)	5.1 [1.54- >7.6]	5.9 [1.80- >7.6]	0.76
- Baseline INR > 7.6 N (%)	35 (35%)	49 (35%)	1.0
ICU admissions at entry, N (%)	12 (12%)	12 (9%)	0.51

VKA, Vitamin K antagonists; INR, International Normalized Ratio; ICU, Intensive Care Unit. Acenocoumarol was the only VKA used besides phenprocoumon. Concomitant antithrombotic drugs: acetyl salicylic acid, clopidogrel, non-steroid anti-inflammatory drugs, and low molecular weight heparins.

Table 2. Indication for PCC treatment and concomitant therapy.

	Fixed dose (n=101)	Variable dose (n=139)	P value
Indication for PCC treatment, N (%)			0.73
- Gastrointestinal bleed	58 (57%)	79 (57%)	
- Muscle bleed	9 (9%)	17 (12%)	
- Intraperitoneal or abdominal wall bleed	10 (10%)	8 (6%)	
- Hemoptysis	4 (4%)	5 (4%)	
- Other	20 (20%)	30 (22%)	
Endoscopic treatment of total GI bleeding complications, N (%)	27 (47%)	33 (42%)	0.60
Invasive procedure for all non-GI bleeding complications, N (%)	15 (35%)	20 (34%)	1.00
Use of hemostatic drugs, N (%)	10 (10%)	6 (4%)	0.12
Transfusion of RBC, N (%)	62 (62%)	92 (66%)	0.50
Transfusion of FFP, N (%)	15 (15%)	12 (9%)	0.15
Mortality during hospitalization	14 (14%)	36 (26%)	0.025

Other indications for PCC treatment were: anemia and hemoglobin decrease in unstable patient (5 fixed dose, 8 variable dose), severe epistaxis (1 fixed dose versus 6 variable dose), bleeding complications at the surgery site (4 fixed dose vs. 6 variable dose), severe haematuria (1 fixed dose vs. 2 variable dose), multiple bleeds after a fall (2 fixed dose, 1 variable dose), hemothorax (1 in each cohort), severe vaginal bleeding (2 fixed dose vs. 1 variable dose), leaking dialysis shunt (2 fixed dose), kidney bleed (1 fixed dose), sigmoid perforation (1 fixed dose), ruptured aneurysm (3 variable dose), hemartosis (1 variable dose), and intraocular bleed (1 variable dose). Hemostatic drugs consisted of: desmopressin, protamin, and tranexamic acid. Activated factor VII was not used in either cohort. RBC: red blood cells; FFP: fresh frozen plasma.

patients in the fixed dose and the variable dose cohorts, respectively, resulting in a risk difference of -2.99% (90% CI: -8.64 to 2.66) for non-inferiority with the limit set to 4%, indicating that non-inferiority was not established (Table 3).

In the fixed dose cohort, median INR declined from 5.1 (range 1.5 to above 7.6) at baseline to 1.5 (range 1 to 2.9) and in the variable dose cohort, from 5.9 (range 1.8 to above 7.6) to 1.4 (range 0.9 to 3.4), after PCC treatment (Figure 2).

Furthermore, the results on the planned subgroup analysis of baseline INR below 5 showed that non-inferiority was established for the subgroup of patients with a baseline INR below 5 (risk difference 1.9%, 90% CI: -1.2 to 5.1; $P < 0.001$).

An additional *post hoc* analysis showed that non-inferiority of the fixed dose was reached in all patients with a baseline INR below 7.5; this was 64% of the total population (risk difference 1.9%, 90% CI: -2.4 to 6.1; $P < 0.01$).

Data were also analyzed applying a reached INR of less than 1.5, which is often used internationally. This target INR was reached by 51% of patients in the fixed dose cohort and 62% of patients in the variable dose cohort. The results of the baseline INR analyses and the target INR differentiation are reported in Table 4.

Clinical outcome

Successful clinical outcome was seen in 97 of 101 (96%) patients in the fixed dose cohort *versus* 122 of 139 (88%) in the variable dose cohort, with a risk difference of 5.8% ($P < 0.001$). This indicates non-inferiority of the fixed dose

versus the variable dose in the overall data, independently of the reached INR (Table 3).

Prothrombin complex concentrate dose in relation to body weight and clinical outcome

Regarding PCC dose expressed in units F IX per kilogram body weight and clinical outcome, no significant differences were seen between the dosage infused to patients with a positive clinical outcome *versus* patients with a negative clinical outcome within each cohort. In the fixed dose cohort, patients with a positive clinical outcome were treated with a median of 13.2 IU F IX/kg (range 2.9-28.9) *versus* 14.1 IU F IX/kg (range 8.7-15.5) in those treated in the same cohort with a negative clinical outcome ($P = 0.73$).

In the variable dose cohort, patients with a positive clinical outcome were treated with a median of 21.0 IU F IX/kg (range 8.2-40.0) *versus* 18.8 IU F IX/kg (range 13.0-35.5) in those treated in the same cohort with a negative clinical outcome ($P = 0.95$).

Interestingly, no significant differences were observed in body weight between both cohorts (Table 1).

Time to infusion

Time from hospital admission to infusion was recorded for all patients for whom PCC was ordered in the emergency department, which was 60% of our population. In the fixed dose cohort, median time to infusion was 130 min (90% central range 22-233), whereas in the variable dose regimen cohort, the median time to infusion was 160 min (90% central range 60-320; $P = 0.015$).

Complications

One patient in the variable dose regimen developed a deep venous thrombosis, and one patient died in each cohort because of a thromboembolic complication; overall occurrence of thrombotic complications was 1.3%.

Overall mortality rate during hospitalization was 14 of

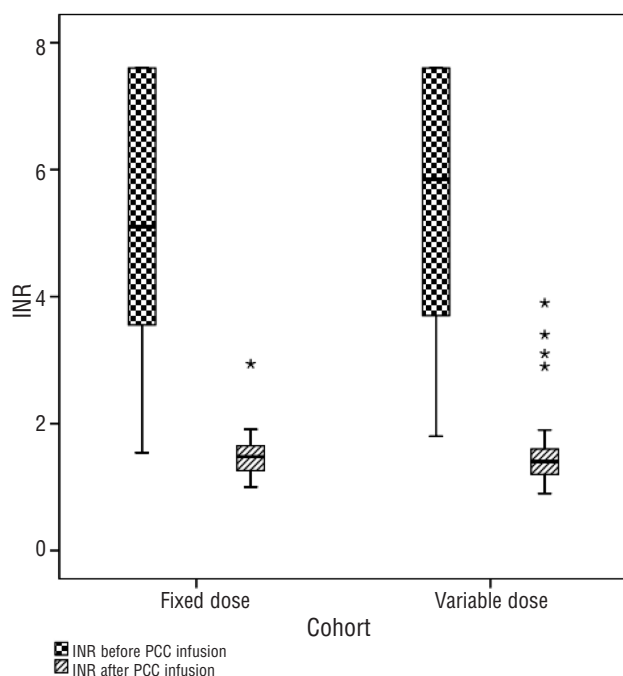


Figure 1. INR before and after PCC treatment. Cohort 1: fixed dose, cohort 2: variable dose regimen. International Normalized Ratio (INR) at baseline and 15 min after PCC treatment. INRs are expressed as a number up to 7.6. INR was above 7.6 in 35% of patients in each cohort. Boxes span the interquartile range. Horizontal lines bisecting the boxes indicate median values and lower and upper error bars the range.

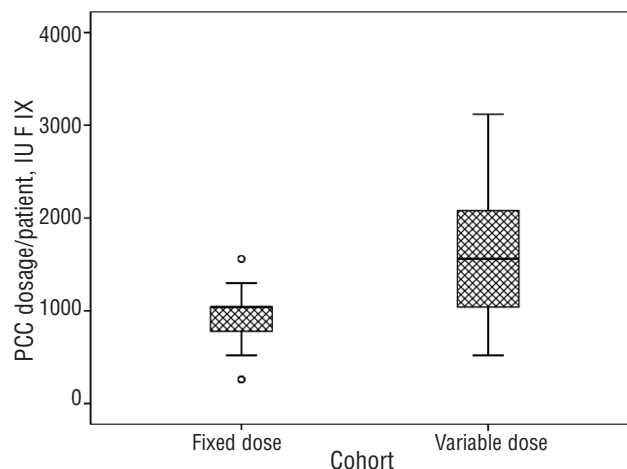


Figure 2. PCC administration. Prothrombin Complex Concentrate (PCC) administered per patient. Graphic conventions as in figure 1. In cohort 1, median dosage is the same line as upper interquartile range. Cohort 1: fixed dose regimen, cohort 2: variable dose regimen.

101 (14%) in the fixed dose cohort *versus* 36 of 139 (26%) in the variable dose regimen ($P=0.025$).

An ongoing bleeding event was fatal in 2 of 14 (14%) patients in the fixed dose cohort and 8 of 36 (22%) in the variable dose cohort ($P=0.70$).

Discussion

This prospective, observational two-cohort study, comparing the treatment outcome of a low fixed PCC dosing regimen of 1,040 IU F IX with the variable PCC dose strategy to rapidly counteract VKA therapy showed that target INR is reached in fewer patients treated with fixed PCC dose (92%) compared to the variable dose regimen (95%), indicating that non-inferiority was not established. In terms of successful clinical outcome, non-inferiority of the fixed dose strategy was established (96% in fixed dose *vs.* 88% in variable dose regimen), independently of the INR.

While the non-inferiority of the low fixed dose is assessed in terms of clinical outcome, independently of the initial INR and the reached INR, we also performed a planned subgroup analysis and a *post hoc* analysis to gain a better understanding of the role and contribution of the baseline INR to clinical outcome.

These analyses showed that the inferiority of the low fixed dose is entirely applicable for those patients with a baseline INR above 7.5. For all patients presenting with a baseline INR up to 7.5, non-inferiority of the low fixed dose for both reaching the target INR as well as clinical outcome is confirmed. Two-thirds of our population presented with a baseline INR below 7.5.

The target INR used in our study is in line with Dutch common practice for non-cranial bleeding emergencies. From an international point of view, it is interesting to know the proportion of patients reaching an INR below 1.5. Therefore, we also considered an analysis that showed that the INR decreases more often below 1.5 with higher doses in the variable dose cohort (Table 4).

Considering the thromboembolic events after PCC treatment, our study showed a very low occurrence of thromboembolic complications in both cohorts (overall 1.2%). Our findings are comparable with other studies in VKA using patients receiving PCC in which thrombotic events were also reported to be rare but still quantifiable.¹⁵⁻²⁰

In the present study, we measured the time to start PCC infusion on patients who were treated with PCC in the emergency department. Our data show a shorter time to infusion, with a median of 30 min, in the low fixed PCC dose regimen. As there was no difference in the availability of PCC or in logistical procedures between the two hospitals, this was probably due to the fact that applying a fixed dose resulted in a shorter time to infusion. This reduction in time could explain our paradoxical results for INR and clinical outcome. It suggests that the critical factor for successful clinical outcome is time to infusion rather than baseline INR. However, this is the first time this phenomenon has been observed and our finding must, therefore, be confirmed in future research, preferably in a randomized setting.

Obviously, the non-randomized design of the study and differences in care and patient population between both participating hospitals are major limitations, and a selection bias cannot be excluded. We thoroughly evaluated possible differences between both cohorts, as shown in

Tables 1 and 2. Analyzing the health status (Charlson Comorbidity Index and history of bleeding events) of patients in both cohorts showed a trend towards more patients in the variable dose cohort having a history of bleeding events, although this was not statistically significant. This difference between both cohorts could have contributed to the lower proportion of patients with a successful clinical outcome and a higher mortality in the variable dosing regimen cohort although, again, this was not statistically significant. All other patients' characteristics were found to be comparable. To prevent misclassification of outcomes, we defined *a priori* successful clinical outcome using the same objective criteria in both hospitals. Interestingly, we saw the same trend in difference in mortality rate in our previous pilot study which was performed in one Dutch hospital site when switching from the variable dose regimen to a low fixed dose regime.¹¹ While bleeding was not a direct cause of death in the majority of patients, it could have a potential prognostic implication as a predictor of poor outcome in clinical assessments. An in depth study has been made of bleeding complications after, for example, bone marrow transplantation.²¹

Because of the observational design of our study, our patient population represents daily clinical practice in an emergency setting. This also includes non-adherence to

Table 3. Overall results.

	Fixed dose (n=101)	Variable dose (n=139)	Proportion difference or P value
Target INR reached, N (%)	88 (91.7%)	124 (94.7%)	-2.99% (90 % CI: -8.6 - 2.7)
Successful clinical outcome, N (%)	97 (96%)	122 (88%)	8.27 % (90 % CI: 2.7 - 13.9)
PCC dosage in F IX/patient, median [range]	1040 IU [260-1560]	1560 IU [520-3120]	**P<0.001
INR after PCC treatment, median [range]	1.48 [1-2.94]	1.40 [0.9-3.40]	*P=0.018
Time to infusion in minutes, median [90% central range]	130 [22-233]	160 [60-320]	*P=0.015

The INR after PCC treatment is missing in 5 (5.0%) patients in the fixed dose cohort and 8 (5.6%) in the variable dose regimen.

Table 4. Results on INR.

	Fixed dose (n=96)	Variable dose (n=131)
Target INR < 2.0 reached, N (%)	88 (91.7%)	124 (94.7%)
Baseline INR > 7.5, N	35	45
- Target INR reached, N (%)	28 (80%)	41 (91%)
Baseline INR 5.0-7.5, N	15	34
- Target INR reached, N (%)	14 (93%)	32 (94%)
Baseline INR < 5.0, N	46	52
- Target INR reached, N (%)	46 (100%)	51 (98%)
Reached INR		
- Reached INR < 1.5, N (%)	49 (51%)	81 (62%)
- Reached INR 1.5 - 2.0, N (%)	39 (41%)	43 (33%)
- Reached INR > 2.0, N (%)	8 (8%)	7 (5%)

The INR after PCC treatment is missing in 5 (5.0%) patients in the fixed dose cohort and 8 (5.6%) in the variable dose regimen.

the dosage, as according to hospital protocols. This is illustrated by the range of the median PCC dosage, especially in the fixed dose cohort. Since the aim of the study was to analyze daily clinical practice, we included all patients treated with PCC despite the abovementioned non-adherence. Importantly, in the fixed dose cohort, non-adherence resulted in the vast majority of patients being administered lower PCC doses than the indicated 1,040 IE F IX (median 520 IU F IX). Non-adherence, therefore, did not exert a favorable influence on the results for the fixed PCC dose over the variable dose.

Despite 60 years of experience, there is still considerable heterogeneity in consensus guidelines for the treatment of VKA-associated bleeding. Given the lack of evidence for adequate dosing strategies, a delayed start of treatment is being considered in the critical care setting. Even though new oral anticoagulants are entering routine clinical practice, it is likely that VKA and PCC will still be used extensively over the next few years (and possibly longer). Therefore, the need for well-defined strategies for emergency PCC therapy is still relevant,²² particularly since PCC may be used as an antidote for some of the new oral anticoagulants.²³

Although the low fixed dose is inferior in reaching the target INR in patients with a baseline INR above 7.5, we advocate immediate treatment of all patients entering the

emergency department with a major or clinically relevant VKA-associated non-intracranial bleeding event with a low fixed dose of 1,040 IU F IX. This speeds up the treatment procedure and is non-inferior with regard to successful clinical outcome compared with the variable PCC dose. An additional PCC dose can be considered as soon as the baseline INR measurement has been reported.

Conclusions

The non-inferiority of the fixed PCC dose of 1,040 IU F IX based on the proportion of patients reaching the target INR of less than 2 has not been established. Regarding successful clinical outcome, non-inferiority of the fixed dose strategy has been established independently of baseline INR for all patients, with time to start PCC infusion shortened by a median of 30 min.

Authorship and Disclosures

The information provided by the authors about contributions from persons listed as authors and in acknowledgments is available with the full text of this paper at www.haematologica.org.

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